Measuring trends in prevalence and incidence of HIV infection in countries with generalised epidemics

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Objective: Review of recent data and practice to derive guidance on questions relating to the measurement and analysis of trends in HIV prevalence and incidence.

Results: HIV prevalence among pregnant women attending antenatal clinics (ANCs) remains the principal data source to inform trends in the epidemic. Other data sources are: less available, representative of a small section of the population (sex workers, occupational groups), subject to additional bias (for example, voluntary counselling and testing service statistics), or are not yet available for multiple years (national surveys). Validity of HIV prevalence results may change over time due to improvements in HIV tests per se and implementation of laboratory quality assurance systems. The newer laboratory tests for recent infections require further validation and development of methodology to derive estimates of HIV incidence.

Conclusions: Issues to consider during statistical analyses of trends among ANC attendees are: inclusion of consistent sites only, use of confidence intervals, stratification by site when performing a statistical test for trend, the need for at least three observations in a surveillance system with data collection every one to two years, and sound judgement. Trends in HIV prevalence among pregnant 15–24 year olds attending ANCs can be used to approximate trends in incidence. Indepth small area research studies are useful to inform the interpretation of surveillance data and provide directly measured trends in prevalence and incidence. Modelling can assess changes over time in prevalence, incidence, and mortality at the same time. Modelling tools need to be further developed to allow incorporation of estimates of HIV incidence and mortality, as these data are likely to become available in the future. To increase their explanatory power, models should also be extended to incorporate programmatic inputs.

In recent years, a number of countries with generalised epidemics have observed a decline in HIV prevalence,[1] following the decade-long decline in Uganda.[2 3] In November 2004, the Joint United Nations Programme on AIDS (UNAIDS) Reference Group on Estimates, Modelling and Projections organised a meeting on ''Evidence and causes of declines in HIV prevalence and incidence in countries with generalised epidemics'' in Harare, Zimbabwe, where new data and analyses were presented. These new observations raise questions about whether the HIV prevalence declines are genuine or the result of measurement bias. If real, there are additional questions regarding whether the prevalence declines are the result of a decline in incidence or due to rising mortality rates overtaking the rate of new infections.

Over the years, surveillance systems have expanded with an increase in the number of surveillance sites, specifically in rural areas, along with improvements in the quality of laboratory tests for HIV and testing strategies. In some countries past suggestions of declines in HIV prevalence have in fact been due to these improvements. It is important to distinguish these artefactual HIV prevalence declines from genuine declines.

In the absence of a reliable laboratory based test for recent HIV infections that allows a calculation of HIV incidence, HIV prevalence among 15–24 year old pregnant women has been proposed as a proxy measure for incidence, and is being used to monitor progress against international goals.[4] Considerable experience has now been gained in using prevalence among young pregnant women to monitor trends. In addition, new tests to detect recent HIV infections have become available that can be used to calculate a direct measure of HIV incidence.[5]

This paper reviews relevant recent data and practice to derive guidance on the above questions relating to the measurement and analysis of trends in HIV prevalence and incidence. It also provides recommendations for the further development of methods and for research that could contribute to the interpretation of data related to HIV prevalence and incidence.

DATA SOURCES

Sentinel surveillance among pregnant women attending antenatal clinics (ANCs) has been the major source of data for monitoring HIV prevalence levels and trends in countries with generalised epidemics.[1] Many countries have long series of ANC surveillance data going back to the early 1990s. ANC surveillance systems have evolved in most countries with an initial focus on urban areas and a more recent expansion in rural areas.

The delivery of services like the prevention of mother-to-child transmission (PMTCT) and voluntary counselling and testing (VCT) has provided an opportunity to collect data on HIV prevalence. However, the data from these sources have to be interpreted with caution as they may be subject to bias. This is more problematic for VCT data than for PMTCT data.

Abbreviations: ANC, antenatal clinic; EPP, Estimation and Projection Package; HIV, human immunodeficiency virus; PMTCT, prevention of mother-to-child transmission; VCT, voluntary counselling and testing

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A study in Uganda comparing prevalence trends among VCT clients and ANC attendees has shown that although the prevalence was higher in VCT, the overall trends were similar.[6] Data from VCT programmes should generally not be used to monitor trends in prevalence in the community, as important temporal changes in numbers and characteristics of VCT attendees are likely, especially in relation with the introduction and scaling up of antiretroviral treatment programmes.[7]

It has been suggested that data routinely collected from PMTCT programmes be used to monitor prevalence trends. In the era of increasing access to treatment some have questioned the ethics of continuing with anonymous testing. Data from PMTCT has inherent participation bias as the women accepting the test may be different from those declining. These differences may be related to the risk of infection and the varying quality of counselling. A study in Dar-es-Salaam has shown that age, economic status, marital status, and the number of children living at home affected the likelihood of a woman to accept a test.[8] Two recent studies in Uganda suggest that PMTCT data closely approximate prevalence among all ANC attendees only if PMTCT participation rates are high.[9 10] Additional research on this relation and continued monitoring of uptake of PMTCT services is therefore required to assess further the possible role of HIV prevalence data from PMTCT programmes to monitor trends in the epidemic.

Prevalence data have also been collected from groups with high risk behaviours like female sex workers, their clients, truck drivers, military and police personnel, and STI clinic attendees. Data from these populations are most useful in countries with a concentrated epidemic. Even in countries with a generalised epidemic, some of these groups can contribute disproportionately to the spread of the epidemic (notably sex workers and their clients), and it is important to be able to discern real trends in prevalence in these groups and explain them. Data from screening of military recruits for HIV are a good source of data for young men. These data could also be used as a proxy for measuring incidence. However, these data are not widely available, and the trends in this group may not be generalisable to the wider population.

Monitoring prevalence among blood donors was one of the early surveillance systems put in place. However, data from this source are particularly prone to bias. Indeed, over time blood transfusion services have changed their policies regarding eligibility for blood donation. Blood donors in recent years are therefore likely to be at lower risk of HIV infection compared with those in earlier years, resulting in bias. Screening of repeat blood donors can provide an opportunity to monitor trends in HIV incidence in this group. However, these trends may not be generalisable to the wider population, as their behaviour is likely to differ from the general population given their knowledge of their sero status.

Several countries have conducted national prevalence surveys in the general population in recent years[11] and the number of countries conducting these surveys is expected to increase further. General population surveys have the advantage of drawing on a representative sample of the country's population and provide data for men. However, they do not provide data on non-household populations such as the military, sex workers, students, and persons living in individual settings. Response rates impact on the quality of the result. It is not enough to measure the overall response rate; it is also needed to investigate possible bias introduced by the absence of potential participants or by refusal to take the HIV test.[12] General population surveys are expensive and therefore are conducted after long intervals. As a result, most countries currently have only one data point, although many countries are expected to have two or more data points by the end of the decade. These data cannot, therefore, currently be used to show trends but may be used for this purpose in the future. When several data points will become available, it will be important to consider the effect of any changes in methodology between rounds of the national surveys, as well as changes in bias introduced by non-response and the effect on prevalance of an increasing number of people on antiretroviral treatment in the future.[11]

In conclusion, ANC surveillance is likely to remain the primary data source to monitor trends in HIV prevalence in countries with generalised epidemics. Because ANC surveillance has been conducted over a long period, it presents unique opportunities for analysis of trends in prevalence starting from the initiation of the surveillance system.

LABORATORY ISSUES

Important as it is to document the quality of surveillance data in current years, for the analysis of trends in HIV prevalence it is also important to try to establish the validity of HIV surveillance data from past years. The intrinsic validity of HIV tests in recent years has improved considerably.[13] In addition, many countries have instituted quality assurance schemes that increase the validity of the HIV testing for surveillance in the field.[14] For example, a few years ago in Zimbabwe an apparent decline in prevalence observed in ANC surveillance was due to improvements in the quality of the laboratory system, with an important number of false positive tests in the early years of the surveillance system.[15] As a result of improved tests and improved quality assurance systems in countries where additional resources have become available for HIV surveillance, the HIV surveillance data in recent years have better validity than those from earlier years. To account for the less valid results in past years, in a statistical test for linear trend,[16] more weight could be given to the better quality data from recent years. Alternatively, if the period is of interest, one could limit the trend analysis to those years where data are known to be of high quality. Still, for the purpose of HIV prevalence trend analysis, it is important to have information on trends of up to 10 years ago as trends in HIV prevalence at that time will determine current trends in mortality.[17 18]

With regard to results for tests for recent HIV infections, assays have only recently become available. The sensitive/less sensitive testing algorithm was never fully validated for subtypes other than B,[19] and experience with the IgG capture BED-enzyme immunoassay (BED-CEIA) has only started recently.[5 20] Hence, there is little experience with assessing trends in these types of data. When testing stored samples to assess trends in incidence in past years, it is again possible that results from stored samples will be less valid compared with those from fresh samples. These data could be treated in a similar way as proposed above for data from earlier years when quality assurance was less rigorous or absent.

Laboratory methods may be different for different groups under surveillance, and for HIV prevalence data from services. For example, recommended testing algorithms for unlinked anonymous surveillance in high prevalence countries are less stringent than algorithms for diagnostic testing, whether in PMTCT programmes or in free-standing VCT centres.[21] This raises issues of comparability of results from different sources.

MEASURING PREVALENCE TRENDS AMONG PREGNANT WOMEN ATTENDING ANCs

HIV prevalence among ANC attendees continues to be a good approximation of HIV prevalence in the general population.[22] In several countries recent estimates of national prevalence, based on ANC surveillance data, have been lower than

estimates in earlier years, coinciding with an extension of the surveillance system to rural areas. In most cases there has not been a real decline in prevalence, but the lower prevalence is due to the prior underrepresentation of rural areas in the surveillance system combined with the fact that rural areas tend to have lower prevalence. For example in Ethiopia, national prevalence was estimated at 6.4% in 2001 but only 4.4% in 2003.[23 24] However, as described in the accompanying paper in this supplement, the epidemic in Ethiopia is likely to still be expanding because of prevalence increases in rural areas.[25] Therefore the apparent decline in national prevalence is an artefact due to the more representative ANC surveillance system in 2003. To avoid this bias, analyses of HIV prevalence trends in ANC sites should be restricted to those sites with consistent reporting over time.

The analysis of trends should consider the magnitude of any change over a period of consistent data collection. As a rule of thumb, at least three data points showing a consistent trend in prevalence are needed to conclude there is a declining trend. Since most surveillance systems collect data every one to two years, the time spanning the data points should be at least three to six years. Confidence intervals about prevalence estimates should be presented and statistical tests should be used to assess the significance of trends.[16] Test for trend analyses should be stratified by site. Statistical tests should be used with proper judgement, since statistical significance does not necessarily mean importance or relevance.

In general, the period of most interest for evaluation of a decline in prevalence will be some years after HIV prevalence has peaked, since the natural dynamics of an epidemic would lead to a peak in prevalence followed by a short decline and levelling-out of prevalence.[26] A sustained decline in prevalence due to behavioural change could take place immediately following the ''natural'' peak or during the levelling-out period.

APPROACHES TO ASSESSING TRENDS IN HIV INCIDENCE

Three methods are available to assess trends in HIV incidence:

- estimating incidence based on the proportion of recent infections
- modelling incidence from observed prevalence over time
- using HIV prevalence among 15–24 year old pregnant women as an indicator for HIV incidence.

As discussed above, assays for the detection of recent infections, such as BED-CEIA,[5 20 27] are promising but these methods need further validation. Additional validation is needed for subtypes other than B. Furthermore, if these methods are to be applied on ANC samples, analyses are needed to understand the relation between incidence among pregnant women and incidence in the general population. Although HIV prevalence among pregnant women attending ANCs has been shown to be similar to HIV prevalence among the general population in many countries,[22] the same equivalence has not been demonstrated for incidence. A recent study in Uganda has suggested that incidence among pregnant women is higher than among non-pregnant lactating women and non-lactating women.[28] This needs to be further studied in other settings. The statistical considerations regarding the measurement of incidence trends are similar to those for prevalence trends discussed above:

- consistent sites only
- use of confidence intervals
- stratification by site when performing a statistical test for trend
- need for at least three observations.

In addition, since new infections are relatively rare events, much larger sample sizes are needed than for analyses of prevalence trends. Furthermore, since incidence rates can change more rapidly than prevalence rates (which result from the effects of changes in incidence and mortality on past prevalence), more frequent measurement is needed to detect changes in incidence than in prevalence.

In recent years, methods and software have been developed to analyse surveillance data from different sites and years. The Estimation and Projection Package (EPP) fits a smooth curve of adult HIV prevalence to a time series of observations of prevalence, using a mathematical formulation that reflects the dynamics of the epidemic, thereby allowing the underlying trends in incidence and HIV related mortality to be estimated.[29] The Spectrum package uses the HIV prevalence over time together with demographic information and epidemiological assumptions to model age specific HIV prevalence, and incidence and mortality rates and numbers.[30] EPP is attuned to capturing long term changes in incidence that would arise as the result of gradual and sustained behavioural modification, and has the advantage of allowing for the interdependence of prevalence, incidence, and mortality. This is important because the natural course of HIV epidemics includes a peak and a short term decline in HIV prevalence followed by a plateau, which is a result of the increased mortality rate among infected persons (which lags some 10 years behind the peak in new infections) gradually coming into balance with the incidence rate.[26] EPP and Spectrum therefore allow the user to examine trends in incidence that include a due allowance for the natural dynamics of the epidemic.

Trends in ANC prevalence among 15–24 year olds can be used to approximate trends in incidence.[4] Since most members of this age group will have started their sexual activity only recently, prevalence in this age group will represent relatively recent infections. While this is generally considered a valid approach, the method is imperfect. HIV prevalence trends in young pregnant women may not be representative of trends in all young people and the prevalence in the 20–24 year age group may be affected by HIV related reduced fertility and increased AIDS mortality in this group, especially in countries where women's sexual debut is early.[31 32] The magnitude of these effects needs to be further quantified in a variety of settings. The HIV prevalence among 15–19 year olds has also been used in the past,[33 34] although this indicator is also subject to bias related to changes in fertility and sexual debut. Furthermore, in countries where women's sexual debut is late, this age group may be poorly representative. It is therefore recommended that the 15–24 age group is used to monitor prevalence trends, and that the age distribution of those attending ANCs be monitored over time (which requires age reporting by single year of age). Trends in HIV prevalence for women with a first pregnancy at ANC should also be analysed, especially in countries with low levels of contraceptive use.[31]

In general, application of multiple methods will result in a more robust conclusion. Therefore, whenever possible, one should explore trends in incidence using two or three of the above methods:

- detection of recent infections—when the assays will have been sufficiently validated
- modelling of prevalence data
- trend analyses of prevalence in young women or in primigravidae.

SUBNATIONAL AND SMALL AREA TRENDS

Trend analysis of HIV prevalence may be carried out at the national and subnational levels using the data sources discussed earlier. Most surveillance data have been collected in urban sites, and only in recent years has there been a major effort to extend HIV sentinel surveillance to rural sites.[1] Where data are available for urban and rural sites, the national trend analysis can be extended to both urban and rural areas. This analysis will be subject to the limitation that trends can only be assessed in consistent sites. As a result, in many countries trend analysis for rural areas will be constrained by a lack of data from consistent rural sites.

The 2005 version of the EPP explicitly considers trends in individual surveillance sites. Analysis of HIV trends at the subnational geographic divisions of a country should be considered based on the needs of the country, national as well as local, including health planning applications. These geographic divisions comprise primary geographic/political areas (province, state, region, etc.) and secondary political divisions (county, district, commune, etc.) within countries.[35] Definitions of rural and urban areas are specific for each country as they are defined in-country and definitions vary considerably despite the United Nations' efforts to bring some level of standardisation.[36] It is clear that divergent trends in prevalence may operate in different parts of the area of analysis. The analysis of any such trends can only be improved through the extension of the surveillance system with an increasing number of surveillance sites. Differential migration of HIV infected and uninfected persons into and out of regional divisions may need to be considered when analysing changes in prevalence at subnational level.

A number of countries, including Malawi, Uganda, Tanzania, and Zimbabwe have initiated community based longitudinal research studies of HIV.[37–41] By design these studies have taken place in small geographical areas. Research results from these study sites have been invaluable to inform HIV prevention policies and help interpret results from sentinel surveillance. These studies have also allowed to measure trends not only in HIV prevalence but also in HIV incidence. However, levels and trends in these small areas are not readily generalisable to the whole country, as divergent trends may operate in the country. The possibility of changing participation bias in these studies needs to be considered when examining HIV trends. The documentation of similar trends in these research sites and the national data sources will allow more confidence that the observed trends are representative of the true trends in the population.

Key messages

- HIV prevalence among pregnant women attending ANCs remains the principal data source to inform trends in generalised epidemics.
- Analytic methods need to allow for changes in bias over time in ANC prevalence data, including laboratory error, changes in fertility and mortality, and changes in number and characteristics of surveillance sites.
- To inform trends in incidence three possibilities exist: analysis of trends in HIV prevalence among 15–24 year old pregnant women attending ANCs; laboratory tests that detect recent infections which allow the estimation of a measure of incidence; and modelling which can assess changes over time in prevalence, incidence, and mortality at the same time.

DISCUSSION

This overview on trend analysis has raised many issues and potential biases that need to be taken into account when embarking on trend analysis. The most important questions that need to be addressed by analysis of HIV trends is whether the apparent trends in prevalence are real or the result of changing biases and selection effects, and whether it is possible to conclude that any change in incidence has occurred (to be differentiated from declining prevalence because of mortality overtaking incidence).

To assess the contribution of programmes, detailed time series data on programme outputs are needed. A separate paper in this supplement has considered trends in behaviours.[42] As explained by Garnett *et al* in this supplement,[26] there are well studied and widely understood relations between HIV prevalence, HIV incidence, and AIDS mortality. In this paper we have reviewed the major possibilities for analyses of trends in prevalence and incidence. Whereas there are increasing amounts of data on prevalence, assays for the detection of new infections have only recently become available. Limited valid data on mortality and on AIDS-specific mortality are currently available, although new initiatives aim at gathering nationally representative mortality data in many of the countries most affected by AIDS. For both incidence and mortality more data are needed to get a better understanding of the HIV/AIDS dynamics in highly affected countries.

In terms of joint analysis, it is useful to triangulate changes in prevalence, incidence, behaviours, and mortality. Short of putting all these data in a model, it is useful to simply juxtapose the data that relate to these different indicators. In this type of analysis, changes due to programmatic efforts may be evidenced as a deviation from the past incidence trend, with the incidence trend being informed by data on prevalence, and an understanding that mortality affects prevalence and creates a peak in the prevalence curve. A more powerful analysis can be done by modelling, as models can co-examine prevalence, incidence, behaviour, and mortality at the same time.[43]

Further research and development of analytic tools is necessary to improve the analysis of the different data sources, and to provide insight in the contribution of programmes to desired changes in incidence:

(1) Additional validation of assays for recent infection is needed. Validation is needed for additional subtypes as well as for how to analyse samples and data from countries with a mix of subtypes with slightly different window periods. In addition, there is a need for further development of epidemiological methods and interpretation of the data generated by assays for recent infections, including how these data (from ANC samples and in the future from national household surveys) relate to incidence in the general population. Finally, there is a need for the further development of statistical methods for the analysis of new infections, to derive a measure of the incidence rate, generate confidence intervals around these and analyse trends in incidence.

(2) In its guidelines on second generation surveillance, WHO and UNAIDS have recommended using the prevalence among 15–24 year old pregnant women as a proxy for incidence. The country papers in this supplement suggest that this continues to be a useful approach. However, evidence has also emerged to indicate that in the later years in this age band, in addition to reduced fertility there is also an effect of mortality on prevalence.[32] It is therefore important to continue to quantify the effects of these and other biases on the use of trends in HIV

prevalence among 15–24 year old pregnant women as a proxy for trends in incidence in the community.

(3) Models will undoubtedly play an important role in trying to disentangle the effects of mortality and natural history on incidence trends. An effort has been made in a paper in this supplement, with an age-structured model applied to data from a number of countries with generalised epidemics.[43] Existing tools such as EPP and Spectrum need to evolve further to allow direct input of measured incidence and (AIDS specific) mortality data. However, these models do not currently explicitly factor the programmatic inputs in, and this constitutes another area for further developments.

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AUTHORS' CONTRIBUTIONS

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